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# Improved Computation of Natural Logarithm using Chemical Reaction Networks

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**Abstract**—Recent researches have focused on nucleic acids as a substrate for designing biomolecular circuits for *in situ* monitoring and control. A common approach is to express them by a set of idealised abstract chemical reaction networks (ACRNs). Here, we present new results on how abstract chemical reactions, viz., catalysis, annihilation and degradation, can be used to implement circuit that accurately computes logarithm function using the method of Cubic Arithmetic-Geometric Mean (AGM).

**Keywords**—abstract chemical reaction network, DNA strand displacement, natural logarithm, cubic arithmetic-geometric mean

## I. INTRODUCTION

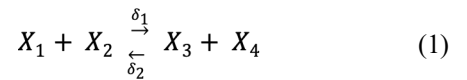
An objective of synthetic biology is to design biomolecular circuits for *in situ* monitoring and control. Recently, nucleic acid reactions have been proposed as a potential solution for these purposes [1 – 4]. A key advantage of nucleic acid reactions consists in the ease and precision with which these can be implemented, as their design relies essentially on the well-known Watson-Crick base-pairing mechanism (i.e. adenine-thymine and guanine-cytosine pairing), which enables precise programming and timing of molecular interactions simply by the choice of relevant sequences. This approach has allowed the implementation of a number of complex circuits based on DNA strand displacement [5], DNA enzyme [6] and RNA enzyme [7] reactions, and has been used for the modelling and implementation of various nucleic-acids-based circuits such as feedback controllers [8] and predator-prey systems [9]. Recently, it has been shown that any *chemical reaction network* can be closely approximated by a set of suitably designed DNA strand displacement reactions [10]. This logic can be extended to approximate a set of linear ordinary differential equations (ODEs) by a set of idealised *abstract chemical reaction networks* (ACRNs) which can then be approximated by a set of suitably designed DNA strand displacement reactions [4].

In order to exchange information with environment and make decisions on their behaviour, living cells use chemical reactions as a mean of communication. It was shown that logarithmic sensing is present in various signal transduction mechanisms of a cell and is related to the concept of fold-change detection. Hence, in order to decode the signals the cell is sending, it is necessary to compute natural logarithm [11 – 13].

In this paper, we present a circuit for computing natural logarithm using the method of Cubic Arithmetic-Geometric Mean and compare its results to those obtained by the method of Quadratic Arithmetic-Geometric Mean, presented by us earlier.

## II. NOTATION AND BACKGROUND RESULTS

To ensure consistency, the notation used in [14] and [4] is used throughout in this paper. For example, a bidirectional (i.e., a reversible bimolecular chemical reaction) is represented as



where  $X_i$  are chemical species with  $X_1$  and  $X_2$  being the reactants and  $X_3$  and  $X_4$  being the products. Here,  $\delta_1$  and  $\delta_2$  denote the forward and backward reaction rates, respectively. A unimolecular reaction features only one reactant whereas a multimolecular reaction features two or more reactants. Degradation of a chemical species  $X$  at rate  $K$  (or conversion of  $X$  into an inert form at a rate  $K$ ) is denoted by  $X \xrightarrow{K} \emptyset$ .

### A. Representing signals using differences of concentrations

Whereas signals in systems theory can take both positive and negative values, biomolecular concentrations (with Molar (M) as unit) can only take non-negative values. Thus, following the same approach suggested in [14] and [4], we represent a signal,  $x$  as the difference in concentration of two chemical species,  $x^+$  and  $x^-$ . Here,  $x^+$  and  $x^-$  are respectively the positive and negative components of  $x$  such that  $x = x^+ + x^-$ . The consequence of adopting this scheme is that there is no unique representation for a particular signal. As an example,  $x = 20$  M can be represented by both  $x^+ = 50$  M and  $x^- = 30$  M or equivalently,  $x^+ = 20$  M and  $x^- = 0$  M. In practice,  $x^+$  and  $x^-$  can be realized as single strand DNA molecules, as illustrated in [4] where these complementary positive and negative components would annihilate each other at reaction rate  $\eta$  (i.e.  $x^+ + x^- \xrightarrow{\eta} \emptyset$ ). A key advantage of using this scheme is that it allows the realization of the “subtraction” operation, as discussed further below.

### B. Realising elementary linear system theoretic operators

In [14], results on how to represent linear system theoretic operations such as gain, summation and integration using idealised abstract chemical reactions are presented and it is shown that only three types of elementary chemical reactions, namely, catalysis, annihilation and degradation are needed for such representations. In [4], this set of elementary chemical reactions is further reduced to only two. We here summarise their main results and refer the interested reader to [14] and [4] for details.

Throughout the rest of the paper, equations with superscript  $\pm$  and  $\mp$  are used as shorthand notations that represent the “+” and “-” individual reactions – for example,  $x_i^\pm \xrightarrow{K} x_i^\pm + x_0^\pm$  should be understood as the set of two reactions:  $x_i^+ \xrightarrow{K} x_i^+ + x_0^+$  and  $x_i^- \xrightarrow{K} x_i^- + x_0^-$ . Likewise, the notation  $x_i^\pm \xrightarrow{K} x_i^\pm + x_0^\mp$  is used to represent the set of two reactions:  $x_i^+ \xrightarrow{K} x_i^+ + x_0^-$  and  $x_i^- \xrightarrow{K} x_i^- + x_0^+$ . For brevity and following [14], we will represent such a set of reactions compactly as  $x_i^\pm \xrightarrow{K} x_i^\pm + x_0^\pm$  and  $x_i^\pm \xrightarrow{K} x_i^\pm + x_0^\mp$ .

As noted in [14], one limitation of representing signals as the difference of concentrations is that the requirement of having the same reaction rate,  $K$ , for both positive and negative components may not be easy to implement experimentally. However, as shown in [14], this requirement can be relaxed if the annihilation rate,  $\eta$  in the annihilation reaction,  $x_0^+ + x_0^- \xrightarrow{\eta} \emptyset$  is chosen to be sufficiently large. Hence, we assume this condition of  $\eta \gg K$  throughout the rest of this paper.

### C. Arithmetic Geometric Mean (AGM)

The *arithmetic geometric mean* (AGM) is a hybrid quantity which is defined by combining the arithmetic and geometric means of two positive numbers. As shown in [16], a cubic iteration to compute the arithmetic mean of two numbers  $w$  and  $g$  is given as:

$$g_{n+1} = \frac{g_n + 2w_n}{3} \text{ and } w_{n+1} = \sqrt[3]{\frac{(g_n^2 + g_n w_n + w_n^2)w_n}{3}}.$$

TABLE I. COMPUTATION OF LN USING AGM

| Computation steps:  |   |
|---------------------|---|
| 1) Initialisation   | $w(0) = 3/x$<br>$g(0) = 1$  |
| 2) Iteration        | $w_{n+1} = \sqrt[3]{\frac{(g_n^2 + g_n w_n + w_n^2)w_n}{3}}$<br>$g_{n+1} = \frac{g_n + 2w_n}{3}$<br>$= AG_3\left(1, \frac{3}{x}\right)$ |
| 3) Compute $\ln(x)$ | $\ln(x) = \frac{4}{3\sqrt{3}} \frac{\pi/2}{AG_3\left(1, \frac{3}{x}\right)}$  |

It is shown in [16] that this cubic iteration to compute the AGM can be used for approximating the natural logarithm as follows:

$$\ln(x) = \frac{4}{3\sqrt{3}} \frac{\pi/2}{AG_3\left(1, \frac{3}{x}\right)} \quad (2)$$

Furthermore, it is proved in [16] that the error in this approximation is of the order of  $x^3 \ln(x)$ . The steps for implementing the computation are listed in Table I. Firstly, we set out the initial values of signals  $w$  and  $g$ , where one signal is set as “ $3/x$ ” and the other is “ $1$ ”. Then we find the *cubic arithmetic geometric mean* of two inputs, after which we can approximate the  $\ln(x)$ . In [18], a quadratic iteration to compute the AGM was utilised to compute  $\ln(x)$ . Our objective in this paper is to modify it in order to obtain a faster convergence and a lower steady-state error.

## III. MAIN RESULTS

Our cubic iteration to approximate the natural logarithm  $\ln(x)$  of a given scalar-valued signal  $x$  is illustrated in Table I. Fig. 1 shows the block diagram of our ACRN circuit for implementing the first two steps in the computation of  $\ln(x)$  as listed in that table. The block diagram of our ACRN circuit to implement the third step in the computation of  $\ln(x)$  as listed in Table I is shown in Fig. 2 – this “ratio computation” circuit performs the accurate division of two scalar-valued signals and was presented by us earlier [17].

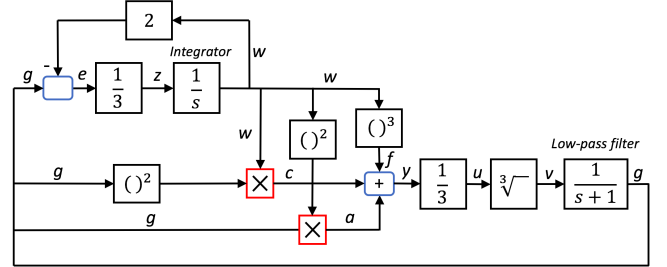


Fig. 1. Block diagram of our circuit to implement the first two steps of the computation of  $\ln(x)$  as described in Table I.

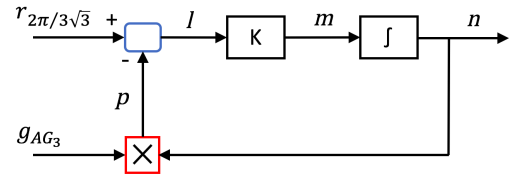


Fig. 2. Block diagram of our circuit to implement the third step of the computation of  $\ln(x)$  as described in Table I.

As can be seen from Fig. 3 and 4, our cubic iteration method converges faster and is more accurate than the method proposed in [18].

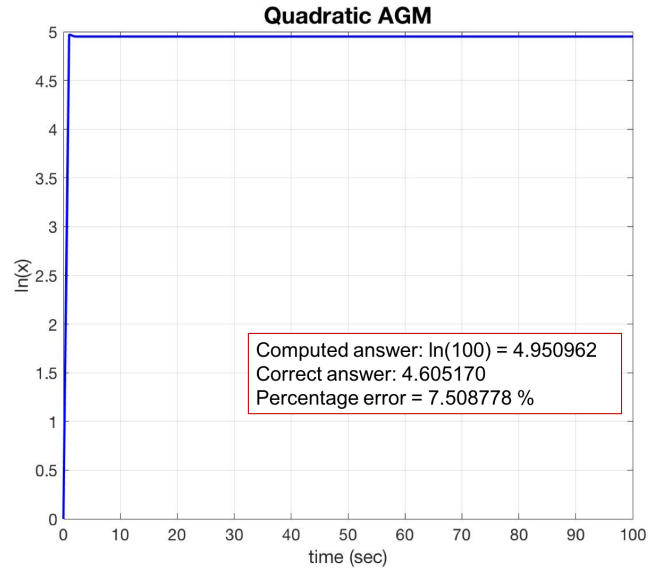


Fig. 3. MATLAB simulation results for computing  $\ln(x)$  via the quadratic iteration of [18];  $x=100$ .

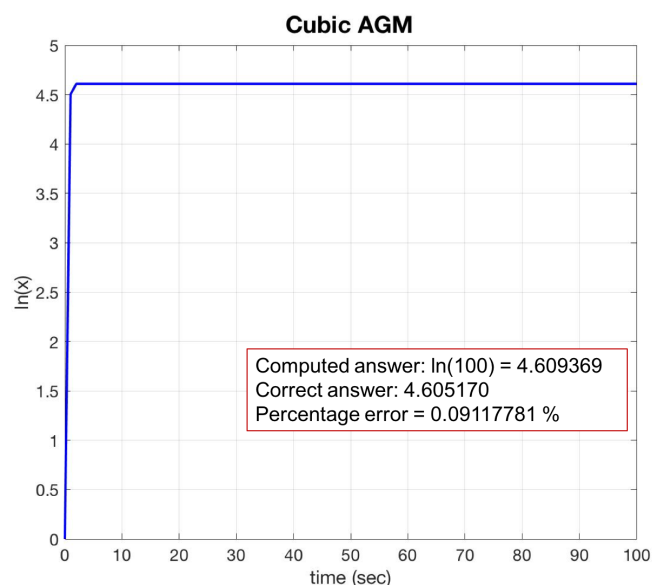


Fig. 4. MATLAB simulation results for computing  $\ln(x)$  via our cubic iteration given in Table I;  $x=100$ .

It has proved in [16], that the quadratic iteration used in [18] to compute  $\ln(x)$  will have a quadratic convergence and the steady-state error of the order of  $x^2\ln(x)$  whereas our cubic iteration to compute  $\ln(x)$  will have a cubic convergence and the steady-state error of the order  $x^3\ln(x)$ . So, our simulation results are not surprising.

Since all the blocks in Fig. 1 and Fig. 2 can be represented by ACRNs, these can be implemented easily using idealised DNA strand displacements (see [4], [17], [18]). All relevant DNA strand displacement reactions, ACRNs and ODEs are noted down in Table II presented in the Appendix section. As of today, it is impossible to build even the simpler circuit of [18] in the wet-lab. The fact that our cubic iteration based circuit is more complex and requires more chemical reactions than the quadratic computation based circuit of [18] carries no adverse implications for the *in silico* Visual DSD implementation, such as the ones described in [4], since the Visual DSD computations will be carried out quite satisfactorily over a normal or high-performance computer.

Unlike Newton's iteration commented upon in [18], the AGM sequence does not correct errors and hence all numbers need to be computed with full precision. In fact, a somewhat greater precision is needed to compensate for accumulated round-off error. Since the two sequences in the AGM become approximately equal after  $k=\ln(\ln(x))/\ln(2)$  iterations, the circuit could be further refined to implement the stop at the end of  $k$  iterations.

## CONCLUSION

We have presented a circuit for computing natural logarithm using the Cubic AGM method, derived by Borwein-Borwein in [16]. We have also derived its equivalent *abstract chemical reaction network* (ACRN) and the ensuing DNA strand displacement representation. Our proposed ACRN computes the natural logarithm with greater speed and accuracy than any existing ACRN – in particular,

we have compared its performance with the ACRN derived in [18] which was shown in [18] to be superior to an ACRN based on Newton's iteration and the variants thereof.

## ACKNOWLEDGMENT

This research is supported, in parts, by the EPSRC INDUSTRIAL CASE AWARD (CASE Voucher 16000070), Microsoft Research, the EPSRC/BBSRC grant BB/M017982/1 to the Warwick Integrative Synthetic Biology Centre, and the Erasmus+ grant to the University of Warwick (Agreement #: 2018-1-UK01-KA107-047454).

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# APPENDIX

TABLE II. COMPUTATION OF LN(X) USING CUBIC AGM: DNA IMPLEMENTATION, THE ACRNs AND THE ODES

| DNA Implementation   | Formal CRNs   | ODEs  |
|--|---|---|
| <b>Block 1</b>   |   |   |
| $\left. \begin{array}{l} g^\pm + G_1^\pm \xrightarrow{\frac{1}{3}q_1} \emptyset + O_1^\pm \\ O_1^\pm + T_1^\pm \xrightarrow{q_{max}} g^\pm + z^\pm \\ w^\mp + G_2^\pm \xrightarrow{\frac{2}{3}q_1} \emptyset + O_2^\pm \\ O_2^\pm + T_2^\pm \xrightarrow{q_{max}} w^\mp + z^\pm \\ z^\pm + G_3^\pm \xrightarrow{q_1} \emptyset + \emptyset \end{array} \right\} \dots$ | $\left. \begin{array}{l} g^\pm \xrightarrow{\frac{1}{3}\gamma_1} g^\pm + z^\pm \\ w^\mp \xrightarrow{\frac{2}{3}\gamma_1} w^\mp + z^\pm \\ z^\pm \xrightarrow{\gamma_1} \emptyset \end{array} \right\}$ | $\dot{z} = \gamma_1 \left( \frac{1}{3}(g - 2w) - z \right)$ |
| $\left. \begin{array}{l} z^+ + L_z \xrightleftharpoons[q_{max}]{q_{max}} H_z + B_z \\ z^- + LS_z \xrightleftharpoons[q_{max}]{q_{max}} HS_z + BS_z \\ z^- + H_z \xrightarrow{q_{max}} \emptyset + \emptyset \end{array} \right\}$  | $z^+ + z^- \xrightarrow{\eta} \emptyset$  |   |
| <b>Block 2</b>   |   |   |
| $\left. \begin{array}{l} z^\pm + G_4^\pm \xrightarrow{q_2} \emptyset + O_4^\pm \\ O_4^\pm + T_4^\pm \xrightarrow{q_{max}} z^\pm + w^\pm \\ w^+ + L_w \xrightleftharpoons[q_{max}]{q_{max}} H_w + B_w \\ w^- + LS_w \xrightleftharpoons[q_{max}]{q_{max}} HS_w + BS_w \\ w^- + H_w \xrightarrow{q_{max}} \emptyset + \emptyset \end{array} \right\}$                    | $\left. \begin{array}{l} z^\pm \xrightarrow{\gamma_2} z^\pm + w^\pm \\ w^+ + w^- \xrightarrow{\eta} \emptyset \end{array} \right\}$   | $\dot{w} = \gamma_2 z$                                      |
| <b>Block 3</b>   |   |   |
| $\left. \begin{array}{l} w^\pm + L_3^\pm \xrightleftharpoons[q_{max}]{q_3} H_3^\pm + B_3^\pm \\ 2g^\pm + H_3^\pm \xrightarrow{q_{max}} O_3^\pm + \emptyset \\ O_3^\pm + T_3^\pm \xrightarrow{q_{max}} \emptyset + w^\pm + 2g^\pm + c^\pm \end{array} \right\}$   | $\left. \begin{array}{l} w^\pm + 2g^\pm \xrightarrow{\gamma_3} w^\pm + 2g^\pm + c^\pm \\ c^\pm \xrightarrow{\gamma_3} \emptyset \end{array} \right\}$   | $\dot{c} = \gamma_3 (w * g^2 - c)$                          |
| $\left. \begin{array}{l} c^\pm + G_5^\pm \xrightarrow{q_3} \emptyset + \emptyset \\ c^+ + L_c \xrightleftharpoons[q_{max}]{q_{max}} H_c + B_c \\ c^- + LS_c \xrightleftharpoons[q_{max}]{q_{max}} HS_c + BS_c \\ c^- + H_c \xrightarrow{q_{max}} \emptyset + \emptyset \end{array} \right\} \dots$   | $c^+ + c^- \xrightarrow{\eta} \emptyset$  |   |
| <b>Block 4</b>   |   |   |
| $\left. \begin{array}{l} g^\pm + L_5^\pm \xrightleftharpoons[q_{max}]{q_4} H_5^\pm + B_5^\pm \\ 2w^\pm + H_5^\pm \xrightarrow{q_{max}} O_5^\pm + \emptyset \\ O_5^\pm + T_5^\pm \xrightarrow{q_{max}} \emptyset + g^\pm + 2w^\pm + a^\pm \end{array} \right\}$   | $\left. \begin{array}{l} g^\pm + 2w^\pm \xrightarrow{\gamma_4} g^\pm + 2w^\pm + a^\pm \\ a^\pm \xrightarrow{\gamma_4} \emptyset \end{array} \right\}$   | $\dot{a} = \gamma_4 (g * w^2 - a)$                          |
| $\left. \begin{array}{l} a^\pm + G_6^\pm \xrightarrow{q_4} \emptyset + \emptyset \\ a^+ + L_a \xrightleftharpoons[q_{max}]{q_{max}} H_a + B_a \\ a^- + LS_a \xrightleftharpoons[q_{max}]{q_{max}} HS_a + BS_a \\ a^- + H_a \xrightarrow{q_{max}} \emptyset + \emptyset \end{array} \right\} \dots$   | $a^+ + a^- \xrightarrow{\eta} \emptyset$  |   |

TABLE II. COMPUTATION OF LN(X) USING CUBIC AGM: DNA IMPLEMENTATION, THE ACRNs AND THE ODEs (CONTINUED)

| DNA Implementation  | Formal CRNs  | ODEs   |
|---|--|--|
| <b>Block 5</b>  |  |  |
| $3w^\pm + G_7^\pm \xrightarrow{q_2} \emptyset + O_7^\pm$<br>$O_7^\pm + T_7^\pm \xrightarrow{q_{max}} 3w^\pm + f^\pm$<br>$f^\pm + G_8^\pm \xrightarrow{q_5} \emptyset + \emptyset$<br>$f^+ + L_f \xrightleftharpoons[q_{max}]{} H_f + B_f$<br>$f^- + LS_f \xrightleftharpoons[q_{max}]{} HS_f + BS_f$<br>$f^- + H_f \xrightarrow{q_{max}} \emptyset + \emptyset$   | $\left. \begin{array}{l} \dots \\ f^\pm \xrightarrow{\gamma_5} \emptyset \end{array} \right\}$ | $\dot{f} = \gamma_5 w^3$                         |
| <b>Block 6</b>  |  |  |
| $f^\pm + G_9^\pm \xrightarrow{\frac{1}{3}q_6} \emptyset + O_9^\pm$<br>$O_9^\pm + T_9^\pm \xrightarrow{q_{max}} f^\pm + u^\pm$<br>$c^\pm + G_{10}^\pm \xrightarrow{\frac{1}{3}q_6} \emptyset + O_{10}^\pm$<br>$O_{10}^\pm + T_{10}^\pm \xrightarrow{q_{max}} c^\pm + u^\pm$<br>$a^\pm + G_{11}^\pm \xrightarrow{\frac{1}{3}q_6} \emptyset + O_{11}^\pm$<br>$O_{11}^\pm + T_{11}^\pm \xrightarrow{q_{max}} a^\pm + u^\pm$<br>$u^\pm + G_{12}^\pm \xrightarrow{q_6} \emptyset + \emptyset$ | $\left. \begin{array}{l} \dots \\ u^\pm \xrightarrow{\gamma_6} \emptyset \end{array} \right\}$ | $\dot{u} = \gamma_6(\frac{1}{3}(f + c + a) - u)$ |
| $u^+ + L_u \xrightleftharpoons[q_{max}]{} H_u + B_u$<br>$u^- + LS_u \xrightleftharpoons[q_{max}]{} HS_u + BS_u$<br>$u^- + H_u \xrightarrow{q_{max}} \emptyset + \emptyset$  | $\left. \begin{array}{l} \dots \\ u^+ + u^- \xrightarrow{\eta} \emptyset \end{array} \right\}$ |  |
| <b>Block 7</b>  |  |  |
| $u^\pm + G_{13}^\pm \xrightarrow{q_7} \emptyset + O_{13}^\pm$<br>$O_{13}^\pm + T_{13}^\pm \xrightarrow{q_{max}} u^\pm + 3v^\pm$<br>$v^\pm + G_{14}^\pm \xrightarrow{q_7} \emptyset + \emptyset$<br>$v^+ + L_v \xrightleftharpoons[q_{max}]{} H_v + B_v$<br>$v^- + LS_v \xrightleftharpoons[q_{max}]{} HS_v + BS_v$<br>$v^- + H_v \xrightarrow{q_{max}} \emptyset + \emptyset$   | $\left. \begin{array}{l} \dots \\ v^\pm \xrightarrow{\gamma_7} \emptyset \end{array} \right\}$ | $\dot{v} = \gamma_7(u^{\frac{1}{3}} - v)$        |
| <b>Block 8</b>  |  |  |
| $v^\pm + G_{15}^\pm \xrightarrow{q_8} \emptyset + O_{15}^\pm$<br>$O_{15}^\pm + T_{15}^\pm \xrightarrow{q_{max}} v^\pm + g^\pm$<br>$g^\pm + G_{16}^\pm \xrightarrow{q_8} \emptyset + \emptyset$<br>$g^+ + L_g \xrightleftharpoons[q_{max}]{} H_g + B_g$<br>$g^- + LS_g \xrightleftharpoons[q_{max}]{} HS_g + BS_g$<br>$g^- + H_g \xrightarrow{q_{max}} \emptyset + \emptyset$  | $\left. \begin{array}{l} \dots \\ g^\pm \xrightarrow{\gamma_8} \emptyset \end{array} \right\}$ | $\dot{g} = \gamma_8(v - g)$                      |

TABLE II. COMPUTATION OF LN(X) USING CUBIC AGM: DNA IMPLEMENTATION, THE ACRNs AND THE ODES (CONTINUED)

| DNA Implementation  | Formal CRNs   | ODEs                               |
|---|---|------------------------------------|
| <b>Block 9</b>  |   |                                    |
| $\left. \begin{array}{l} r^\pm + G_{17}^\pm \xrightarrow{q_9} \emptyset + O_{17}^\pm \\ O_{17}^\pm + T_{17}^\pm \xrightarrow{q_{max}} r^\pm + m^\pm \\ p^\mp + G_{18}^\pm \xrightarrow{q_9} \emptyset + O_{18}^\pm \\ O_{18}^\pm + T_{18}^\pm \xrightarrow{q_{max}} p^\mp + m^\pm \\ m^\pm + G_{19}^\pm \xrightarrow{q_9} \emptyset + \emptyset \\ m^+ + L_m \xrightleftharpoons[q_{max}]{q_{max}} H_m + B_m \\ m^- + LS_m \xrightleftharpoons[q_{max}]{q_{max}} HS_m + BS_m \\ m^- + H_m \xrightarrow{q_{max}} \emptyset + \emptyset \end{array} \right\} \dots$ | $\left. \begin{array}{l} r^\pm \xrightarrow{K\gamma_9} r^\pm + m^\pm \\ p^\mp \xrightarrow{K\gamma_9} p^\mp + m^\pm \\ m^\pm \xrightarrow{\gamma_9} \emptyset \\ m^+ + m^- \xrightarrow{\eta} \emptyset \end{array} \right\}$ | $\dot{m} = \gamma_9(K(r - p) - m)$ |
| <b>Block 10</b>   |   |                                    |
| $\left. \begin{array}{l} m^\pm + G_{20}^\pm \xrightarrow{q_{10}} \emptyset + O_{20}^\pm \\ O_{20}^\pm + T_{20}^\pm \xrightarrow{q_{max}} m^\pm + n^\pm \\ n^+ + L_n \xrightleftharpoons[q_{max}]{q_{max}} H_n + B_n \\ n^- + LS_n \xrightleftharpoons[q_{max}]{q_{max}} HS_n + BS_n \\ n^- + H_n \xrightarrow{q_{max}} \emptyset + \emptyset \end{array} \right\}$  | $\left. \begin{array}{l} m^\pm \xrightarrow{\gamma_{10}} m^\pm + n^\pm \\ n^+ + n^- \xrightarrow{\eta} \emptyset \end{array} \right\}$  | $\dot{n} = \gamma_{10}m$           |
| <b>Block 11</b>   |   |                                    |
| $\left. \begin{array}{l} g^\pm + L_8^\pm \xrightleftharpoons[q_{max}]{q_8} H_8^\pm + B_8^\pm \\ n^\pm + H_8^\pm \xrightarrow{q_{max}} O_8^\pm + \emptyset \\ O_8^\pm + T_8^\pm \xrightarrow{q_{max}} \emptyset + g^\pm + n^\pm + p^\pm \\ p^\pm + G_{21}^\pm \xrightarrow{q_{11}} \emptyset + \emptyset \\ p^+ + L_p \xrightleftharpoons[q_{max}]{q_{max}} H_p + B_p \\ p^- + LS_p \xrightleftharpoons[q_{max}]{q_{max}} HS_p + BS_p \\ p^- + H_p \xrightarrow{q_{max}} \emptyset + \emptyset \end{array} \right\} \dots$   | $\left. \begin{array}{l} g^\pm + n^\pm \xrightarrow{\gamma_{11}} g^\pm + n^\pm + p^\pm \\ p^\pm \xrightarrow{\gamma_{11}} \emptyset \\ p^+ + p^- \xrightarrow{\eta} \emptyset \end{array} \right\}$                           | $\dot{p} = \gamma_{11}(g * n - p)$ |